JOC Article
pubs.acs.org/joc

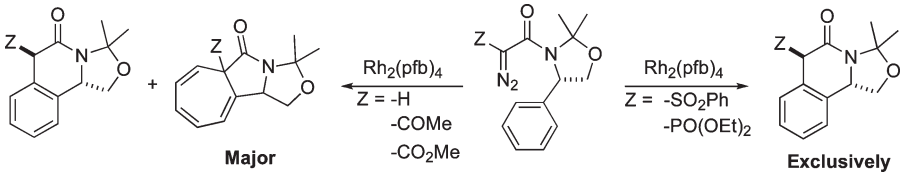
Formal Aromatic C−H Insertion for Stereoselective Isoquinolinone Synthesis and Studies on Mechanistic Insights into the C−C Bond Formation

Chan Pil Park,[†] Advait Nagle,[‡] Cheol Hwan Yoon,[†] Chiliu Chen,[‡] and Kyung Woon Jung*,[†]

[†]*Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089-1661, and* [‡]*Department of Chemistry, University of South Florida, Tampa, Florida 33620*

kwjung@usc.edu

Received June 3, 2009



Formal aromatic C−H insertion of rhodium(II) carbenoid was intensively investigated to develop a new methodology and probe its mechanism. Contrasting with the previously proposed direct C−H insertion, the mechanism was revealed to be electrophilic aromatic substitution, which was supported by substituent effects on the aromatic ring and a secondary deuterium kinetic isotope effect. Various isoquinolinones were synthesized intramolecularly via six-membered ring formation with high regio- and diastereoselectivity, while averting the common Buchner-type reaction. Intermolecularly, dirhodium catalyzed formal aromatic C−H insertion on electron-rich aromatics was also achieved.

Introduction

Isoquinolinones constitute an important class as synthons in the synthesis of many alkaloids[1] as well as chiral ligands for transition metal catalysts.[2] Isoquinolinones bearing a stereogenic center at the C1 position are an extensively studied topic, since they can be used as starting materials in the total synthesis of erysotramidine, peyoruvic acid, and many other compounds. Consequently, much effort has been devoted to the construction of their skeletons by using different methods.[3] Dirhodium(II)-catalyzed C−H insertion of carbenoid compounds has been a powerful and versatile method in synthetic organic chemistry over the past few decades.[4] Recently, much attention has been extended to aromatic C−H insertion systems. Several successful examples of five-membered ring formation without disrupting aromatic resonance have been reported (eq 1).[5] However, in reports for the construction of a six-membered ring, such as isoquinolinone, formation of a 7,5-bicyclic structure via cyclopropanation on the aromatic ring was also observed (eq 2).[6] Although isoquinolinone formation with

(1) (a) Bentley, K. W. *The Isoquinoline Alkaloids*; Hardwood Academic: Amsterdam, The Netherlands, 1998; Vol. 1. (b) Bently, K. W. *Nat. Prod. Rep.* **2001**, *18*, 148. (c) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 742. (d) Hansch, C. P.; Sammes, G.; Taylor, J. B. *Comprehensive Medicinal Chemistry*; Pergamon Press: Oxford, UK, 1990. (e) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.

(2) (a) Durola, F.; Sauvage, J. P.; Wenger, O. S. *Chem. Commun.* **2006**, 171. (b) Sweetman, B. A.; Müller-Bunz, H.; Guiry, P. J. *Tetrahedron Lett.* **2005**, *46*, 4643.

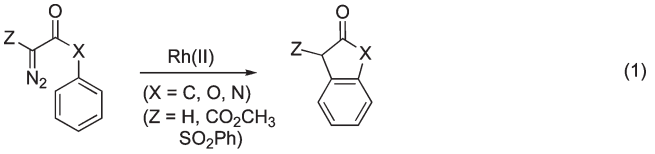
(3) (a) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341. (b) Asao, N.; Yudha, S. S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526. (c) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (d) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (e) Rose, M. D.; Cassidy, M. P.; Rashatasakhon, P.; Padwa, A. *J. Org. Chem.* **2007**, *72*, 538. 21. (f) Garcia, E.; Arrasate, S.; Lete, E.; Sotomayor, N. *J. Org. Chem.* **2005**, *70*, 10368. (g) Tambar, U. K.; Ebner, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11752. (h) Zhang, F.; Simpkins, N. S.; Wilson, C. *Tetrahedron Lett.* **2007**, *48*, 5942. (i) Chaumonte, M.; Piccardi, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2009**, *48*, 179.

(4) (a) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed.* **1994**, *33*, 1797. (b) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (c) Gois, P. M. P.; Afonso, C. A. M. *Eur. J. Org. Chem.* **2004**, 3773. (d) Merlic, C. A.; Zechman, A. L. *Synthesis* **2003**, *8*, 1137. (e) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley and Sons: New York, 1998.

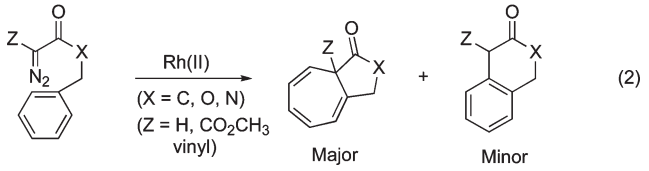
(5) (a) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669. (b) Tsutsui, H.; Yamaguchi, Y.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry*. **2003**, *14*, 817. (c) Hashimoto, S.; Watanabe, N.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1992**, *1508*. (d) Candeias, N. R.; Gois, P. M. P.; Afonso, C. A. M. *J. Org. Chem.* **2006**, *71*, 5489. (e) Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 79. (f) Padwa, A.; Weingarten, M. D. *J. Org. Chem.* **2000**, *65*, 3722.

DOI: 10.1021/jo9011255 Published on Web 07/24/2009

diazoacetamides and protic acid has been reported, the reaction was only applicable to limited substrates and was not regioselective.[7] Variation of the dirhodium(II) ligand system and the α-substituent of the diazo compounds can significantly influence the steric effect and electron density at the rhodium carbenoid center, which in turn has a profound effect on the diastereo- and regioselectivities of the reaction. Therefore, the dirhodium(II) framework has been subjected to ligand exchange with a large number of bridging ligands, and various substituents at the α-position have been examined.[8]

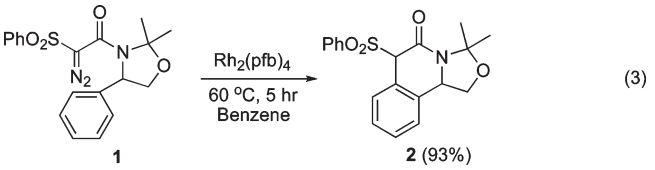


(1)



(2)

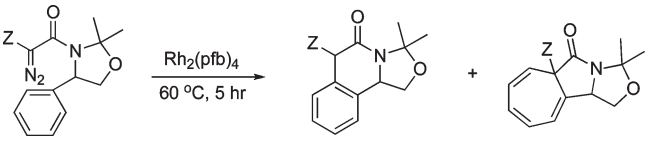
Recently, we reported dirhodium(II)-catalyzed intramolecular C−H insertion of diazoacetamides to afford γ-lactams with high regio- and diastereoselectivities and its application to the total syntheses of rolipram, lactacystin, and kainic acid.[9] We also found that the regio- and chemoselectivity of C−H insertion can be controlled by changing the α-substituent of the carbenoids to an α-(phenylsulfonyl)diazoacetamide group. This encouraged us to investigate an aromatic C−H insertion system, and surprisingly, it was determined that the aromatic α-(phenylsulfonyl)-diazoacetamide compound (**1**) was exclusively converted to isoquinolinone analogue (**2**) by six-membered dirhodium-catalyzed formal aromatic C−H insertion (eq 3).



(3)

Herein, we report a dirhodium-catalyzed formal aromatic C−H insertion for 6,6-bicyclic ring construction and also propose a plausible reaction mechanism, suggesting that this reaction does not resemble direct C−H activation (σ-bond metathesis) such as that of aliphatic C−H insertion. Previously this has been the subject of considerable speculation, due to the lack of experimental data to support the reaction mechanisms.[5,10] Therefore, our newly developed protocols can provide a valuable tool to complement the existing methods, as well as provide mechanistic insight.

TABLE 1. α-Substituent Effect on Rh(II)-Catalyzed Reactions[a]



		products[c]	
entry	Z (α-Substituent)	6,6-bicyclic	7,5-bicyclic
1	H (**3**)		85% (**10**)
2	MeCO (**4**)	12% (**7**)	65% (**11**)
3	MeO_2C (**5**)	15% (**8**)	66% (**12**)
4	PhO_2S (**1**)	93% (**2**)	
5[b]	$(EtO)_2OP$ (**6**)	86% (**9**)	

[a]Reaction conditions: diazoacetamides (1.0 mmol), $Rh_2(pfb)_4$ (5 mol %), benzene (10 mL), 60 °C, 5 h. [b]Reaction time was 12 h, [c]Isolated yields.

Results and Discussion

α-Substituent Effect on the Rh(II)-Catalyzed Aromatic Reaction. We examined formal aromatic C−H insertion reactions of diazoacetamides with different α-substituents such as diazoacetamide **3**, acetodiazoacetamide **4**, and (methoxycarbonyl)diazoacetamide **5** (Table 1). We employed the cyclic *N*,*O*-acetonide substrate to reduce the "degree of freedom" for the rotation of various bonds by forming an *N*,*O*-acetal.[9b] The geminal dimethyl structure in the *N*,*O*-acetal would encounter a steric repulsion with the bulky rhodium(II) carbenoid, thus forcing the aromatic ring to be located proximal to the reactive carbenoid center. This would thereby increase the rate of reaction as well as avoid the formation of undesired side products.[11] The formal aromatic C−H insertion product for diazoacetamide **3** was not detected. Isoquinolinone products were obtained as minor products for carbenoids **4** and **5** and the major products of the reactions were cycloheptapyrrolones **10**, **11**, and **12**. The major products were formed via ring expansion of the cyclopropanated intermediate as the Buchner reaction.[6]

Analogous to our approach toward aliphatic C−H insertion, we postulated that a bulky "relatively electron-rich" carbenoid as a α-substituent would enable a thermodynamically controlled reaction pathway, while averting

(6) (a) Merlic, C. A.; Zechman, A. L.; Miller, M. M. *J. Am. Chem. Soc.* **2001**, *123*, 11101. (b) Wee, A. G. H.; Duncan, S. C. *Tetrahedron Lett.* **2002**, *43*, 6173. (c) Kane, J. L.; Shea, K. M.; Crombie, A. L.; Danheiser, R. L. *Org. Lett.* **2001**, *3*, 1081. (d) Doyle, M. P.; Protopopova, M. N.; Peterson, C. S.; Vitale, J. P.; Mckervey, M. A.; Garcia, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 7865. (e) Yang, M.; Webb, T. R.; Livant, P. *J. Org. Chem.* **2001**, *66*, 4945. (f) Sugimura, T.; Im, C. Y.; Sato, Y.; Okuyama, T. *Tetrahedron* **2007**, *63*, 4027.

(7) Rishton, G. M.; Schwartz, M. A. *Tetrahedron Lett.* **1988**, *29*, 2643.

(8) (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Wee, A. G. H.; Liu, B.; Zhang, L. *J. Org. Chem.* **1992**, *57*, 4404. (c) Moody, C. J.; Miah, S.; Slawin, A. M. Z.; Mansfield, D. J.; Richards, I. C. *Tetrahedron* **1998**, *54*, 9689. (d) Prein, M.; Manley, P. J.; Padwa, A. *Tetrahedron* **1997**, *53*, 7777. (e) Davies, H. M. L.; Jin, Q.; Ren, P.; Kovalenvsky, A. Y. *J. Org. Chem.* **2002**, *67*, 4165. (f) Davies, H. M. L.; Coleman, M. G.; Ventura, D. L. *Org. Lett.* **2007**, *9*, 4971.

(9) (a) Yoon, C. H.; Jaworotko, M. J.; Moulton, B.; Jung, K. W. *Org. Lett.* **2001**, *3*, 3539. (b) Yoon, C. H.; Flanigan, D. L.; Chong, B. D.; Jung, K. W. *J. Org. Chem.* **2002**, *67*, 6582. (c) Yoon, C. H.; Nagle, A.; Chen, C. L.; Gandhi, D.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2259. (d) Flanigan, D. L.; Yoon, C. H.; Jung, K. W. *Tetrahedron. Lett.* **2005**, *46*, 143. (e) Yoon, C. H.; Flanigan, D. L.; Yoo, K. S.; Jung, K. W. *Eur. J. Org. Chem.* **2007**, 37. (f) Jung, Y. C.; Yoon, C. H.; Turos, E.; Yoo, K. S.; Jung, K. W. *J. Org. Chem.* **2007**, *72*, 10114.

(10) (a) Taber, D. F.; Ruckle, R. E. Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686. (b) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.

(11) For the leading references to a comformational study of *N*-acyloxazolidines, see: (a) Porter, N. A.; Bruhnke, J. D.; Wu, W, X.; Rosenstein, I. J.; Breyer, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 7788. (b) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8631.

(12) For the leading references to other studies with α-diazo-α-phenylsulfonyl compounds see: (a) Wee, A. G. H.; Slobodian, J. *J. Org. Chem.* **1996**, *61*, 2897. (b) Padwa, A.; Straub, C. S. *Org. Lett.* **1999**, *1*, 83. (c) Moody, C. J.; Davies, M. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 9. (d) Monteiro, H. J. *Tetrahedron Lett.* **1987**, *28*, 3459. (e) Takeda, H.; Nakada, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2896.

cycloheptapyrrolone formation via an intramolecular Buchner reaction.[6] We selected phenylsulfonyl[12] and ethoxyphosphoryl[13] groups as the candidates for the reactions. As illustrated in entries 4 and 5, α-(phenylsulfonyl)diazoacetamide **1** was exclusively converted to formal aromatic C−H insertion product **2** without the formation of any appreciable side products, such as cycloheptapyrrolone. Although the reaction proceeded more slowly, diethylphosphate carbenoid **6** also afforded the formation of isoquinolinone **9** in 86% yield. Diazoacetamides **1** and **6**, which included a more bulky and less electron-withdrawing α-substituent than carbonyl substituents, gave high chemoselectivity for formal aromatic C−H activation as the intramolecular C−H insertion reaction.[4c] In addition to the reaction being chemoselective, this ring closure was highly diastereoselective, where the stereochemistry of isoquinolinone **2** at the C7 position was inductively generated by the defined chirality at the C14 position (Figure 1). (*S*)-Diazoacetamide **1** gave the (1*S*,4*R*)-isoquinolinone **2** exclusively.

Optimization of Reaction Conditions. As shown in Table 2, we screened various solvents and temperatures to optimize the conditions of the formal aromatic C−H insertion. Diazoacetamide (**1**) was subjected to formal C−H aromatic insertion reaction in CH_2Cl_2, giving rise to a larger amount of isoquinolinone product **2** under reflux condition than room temperature (entries 1 and 2). The insertion reactions in 1,2-dichloroethane and benzene as solvent were complete in excellent yields after 5 h and the increase in yield was attributed to the higher boiling point of these solvents compared with that of dichloromethane (entries 3 and 4). However, although increasing the temperature accelerated the reaction rate, it also accelerated decomposition of the diazoacetamides to desulfonated products along with other side products (entry 5). The use of $Rh_2(OAc)_4$ instead of $Rh_2(pfb)_4$ also gave the formal insertion product exclusively in lower yields over a longer period of time (entry 6). We also tested this carbon−carbon bond forming reaction under different catalytic conditions (entries 7 and 8). Under protic acid-catalyzed condition of electrophilic aromatic substitution, the generation of isoquinolinone products was insignificant. This outcome confirmed that the Rh(II) catalysts played a pivotal role in the reaction and the uncomplexed ligands had minimal effect on the reaction.[7]

Effect of the Aromatic Substituents. Having established optimized conditions, the effect of various aryl substituents on the aromatic ring such as electron-releasing group, electron-withdrawing group, or halide were examined for the feasibility of the methodology, as shown in Table 3. First, we found that diazoacetamides with methoxyphenyl groups **13**, **14**, and **15** exhibited vastly different reactivities. In the cases of *o*-methoxyphenyl compound **13** and *p*-methoxyphenyl compound **15**, formal C−H insertion reactions proceeded more slowly, leading to predominant formation of side products. On the contrary, *m*-methoxyphenyl compound **14** afforded the desired isoquinolinone product **24** in excellent yield. These results can suggest the reaction occurs by an

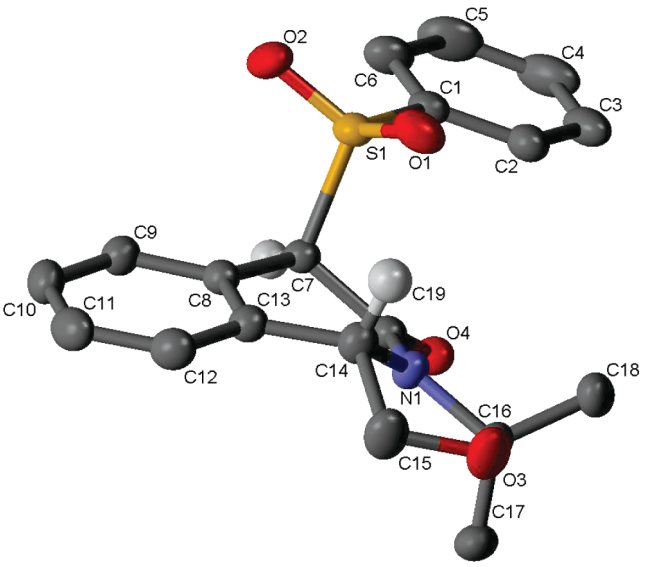


FIGURE 1. Structure of isoquinolinone **2**. H atoms, except those on C7 and C14, are omitted for clarity.

electrophilic aromatic substitution.[14] That is, the site of C−C bond formation for **13** and **15** was mismatched with the π-electron density for an ortho-, para-directing methoxy group in electrophilic aromatic substitution. Additionally, invoking an electrophilic aromatic substitution mechanism is consistent with a five-membered aromatic reaction of diazoacetamides as a favorable reaction pathway when the ortho-position of the aromatic ring is highly activated for electrophilic aromatic substitution, due to the amide nitrogen.[15] The failure of six-membered cyclization to occur for the 2,4-dimethoxyphenyl compound **16** was due to the steric repulsion between the $-OCH_3$ group and the bulky rhodium carbenoid (entry 4).

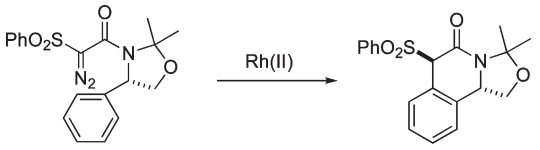
We also evaluated aromatic compounds **18**, **19**, and **20** containing a deactivating $-CF_3$ group. The isoquinolinone formation was successful for only *p*-trifluoromethylphenyl diazoacetamide **20**, which was also consistent with electrophilic aromatic substitution (electron-withdrawing and meta-directing in the substitution) (entry 8). Even though the diazoacetamide **18** was well matched for the construction of isoquinolinone product based on the electrophilic aromatic substitution mechanism, the bulky $-CF_3$ group blocked the approach of the rhodium carbenoid. Next, *m*-fluorophenyl diazoacetamide compound **21** and *p*-fluorophenyl compound **22** were subjected to the formal aromatic C−H insertion (entries 9 and 10) to evaluate the feasibility of a reaction involving aromatic compounds containing halogen functionality. As postulated, diazoacetamide compound **21** gave an increased conversion of isoquinolinone product **29** for the reason that halide groups are deactivating and ortho- and para-directing in electrophilic aromatic substitution. Even though the *N*,*O*-acetal moiety of diazoacetamides is a weakly electron-donating alkyl group, it did not effect a large influence on site selectivity of the aromatic substitution.

(13) For the leading references to other studies with α-diazo-α-alkoxyphosphoryl compounds see: (a) Davis, F. A.; Bowen, K. A.; Xu, H.; Velvadapu, V. *Tetrahedron* **2008**, *64*, 4174. (b) Davis, F. A.; Zhang, J.; Qiu, H.; Wu, Y. *Org. Lett.* **2008**, *10*, 1433. (c) Zhang, W.; Romo, D. *J. Org. Chem.* **2007**, *72*, 8939. (d) Xu, C.; Zhang, Y.; Yuan, C. *Eur. J. Org. Chem.* **2004**, *10*, 2253.

(14) Which is more commonly invoked for the activation of C−H bonds by highly electrophilic late transition metal systems. (a) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2180. (b) Zhou, C. X.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3551.

(15) Doyle, M. P.; Shanklin, M. S.; Pho, H. Q.; Mahapatro, S. N. *J. Org. Chem.* **1988**, *53*, 1017.

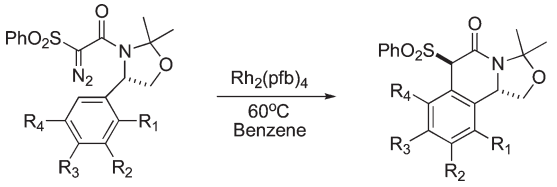
TABLE 2. Optimization of Rh(II)-Catalyzed Formal Aromatic C−H Insertion Reactions[a]



entry	catalyst	solvent	temp (°C)	time (h)	yield (%)[c]
1	$Rh_2(pfb)_4$ (5 mol %)	CH_2Cl_2	rt	72	78
2	$Rh_2(pfb)_4$ (5 mol %)	CH_2Cl_2	reflux	10	88
3	$Rh_2(pfb)_4$ (5 mol %)	$CH_2ClCH_2Cl_2$	60	5	87
4	$Rh_2(pfb)_4$ (5 mol %)	benzene	60	5	93
5	$Rh_2(pfb)_4$ (5 mol %)	Benzene	70	2	69
6	$Rh_2(OAc)_4$ (5 mol %)	BENZENE	60	24	67
7	TFA (10 mol %)[b]	benzene	reflux	10	25
8	$Rh_2(OAc)_4$ (5 mol %) TFA (5 mol %)	benzene	60	5	58

[a]Reaction conditions: diazoacetamide (1.0 mmol) and solvent (10 mL). [b]TFA: trifluoroacetic acid. [c]Isolated yields.

TABLE 3. Effect of Aromatic Substituents[a]



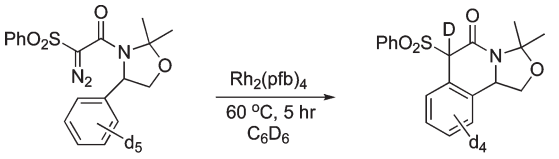
entry	diazoacetamide	time (h)	product[b]
1	**13** (R_1 = OMe, R_2, R_3, R_4 = H)	48	**23** (18%)
2	**14** (R_2 = OMe, R_1, R_3, R_4 = H)	2	**24** (96%)
3	**15** (R_3 = OMe, R_1, R_2, R_4 = H)	48	**25** (10%)
4	**16** (R_1, R_4 = OMe, R_2, R_3 = H)	48	N. R.
5	**17** (R_2, R_3 = OMe, R_1, R_4 = H)	48	**26** (86%)
6	**18** (R_1 = CF_3, R_2, R_3, R_4 = H)	48	N.R.
7	**19** (R_2 = CF_3, R_1, R_3, R_4 = H)	48	**27** (10%)
8	**20** (R_3 = CF_3, R_1, R_2, R_4 = H)	24	**28** (96%)
9	**21** (R_2 = F, R_1, R_3, R_4 = H)	24	**29** (82%)
10	**22** (R_3 = F, R_1, R_2, R_4 = H)	48	**30** (25%)

[a]Reaction conditions: diazoacetamides (1.0 mmol), $Rh_2(pfb)_4$ (5 mol %), benzene (10 mL). [b]Isolated yields.

The reaction site was predominantly influenced by other substituents, such as $-OCH_3$, $-CF_3$, and $-F$.

Secondary Deuterium Kinetic Isotope Effect (SDKIE) for Dirhodium(II)-Catalyzed Formal Aromatic C−H Insertion; Electrophilic Aromatic Substitution. To clarify the mechanism of dirhodium(II)-catalyzed C−C bond formation via formal C−H insertion, we examined the reaction with deuterated diazoacetamide-d_5 **31** in the presence of $Rh_2(pfb)_4$ at 60 °C. As an expected reaction pathway, a diazoacetamide-d_5 **31** study was conducted to confirm a 1,2-hydrogen shift as a result of formal aromatic C−H insertion and then deuterated isoquinolinone **32** was exclusively produced (Scheme 1).[16,17] The reaction rate of this catalysis was found to be the same as

SCHEME 1. Deuterium Transfer in the Rhodium-Catalyzed Reaction of Diazoacetamide-d_5 31



31 **32** (92%)

that of the formal C−H insertion reaction of undeuterated diazoacetamide compound **1**. This result implied that the C−H or C−D bond breaking process would not be included in the overall rate-determining step.

Therefore, to understand the kinetic difference between C−H and C−D, we studied an intramolecular competition reaction using monodeuterated compound **33**. As represented in Scheme 2, we estimated the kinetic isotope effect with diazoacetamide-d_1 **33**, which was prepared from 2′-hydroxyacetophenone.[18] The ratio of deuterated isoquinolinone products **34** and **35** was 46.1%/53.9% and the calculated kinetic isotope effect value for the reaction was 0.855 (k_H/k_D < 1). Because primary isotope effects are expected for direct C−H activation reaction (σ-bond metathesis), not observing a primary isotope effect could rule out a direct C−H activation pathway, such as an aliphatic C−H insertion. The observation of the inverse SDKIE value is consistent with a sp^2- to sp^3-hybridization change during the addition of a rhodium carbenoid to the sp^2-center of the aromatic ring to form a σ-complex adduct as the rate-determining step.[19] This inverse effect would warrant electrophilic aromatic substitution over direct aromatic C−H insertion without ambiguity.

Mechanistic Study Dependent on the α-Substituent of Diazoacetamides. On the basis of these experimental results, we would like to suggest a plausible mechanism for Rh(II)-catalyzed formal C−H insertion to produce stereoselective isoquinolinone as follows (Scheme 3): In the first step, diazoacetamide **1** interacted with dirhodium catalyst to

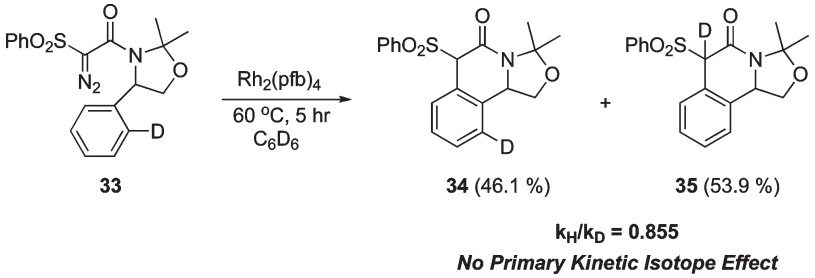
(16) (a) Hoye, T. R.; Dinsmore, C. J. *Tetrahedron Lett.* **1991**, *32*, 3755. (b) Davies, H. M. L.; Saikali, E.; Clark, T. J.; Chee, E. H. *Tetrahedron Lett.* **1990**, *31*, 6299.

(17) Although we confirmed the deuterated product **32** through crude NMR data, the transferred deuterium was lost after column chromatography (see the Supporting Information for NMR spectra). Therefore, the deuterated product **32** would be the kinetically favored one via the proposed transition state before H/D exchange or equilibration (e.g., silica column). Besides, we could not observe the other diastereomer during the reaction.

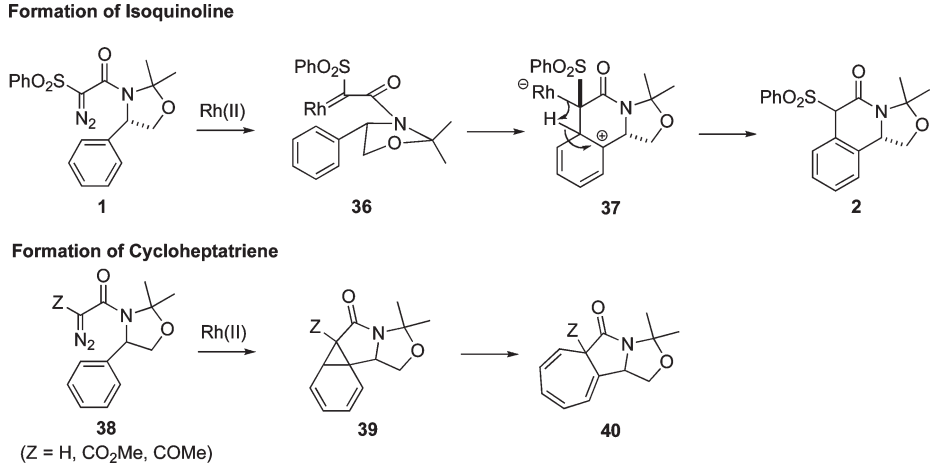
(18) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541.

(19) (a) Griffin, G. W.; Horn, K. A. *J. Am. Chem. Soc.* **1987**, *109*, 4919. (b) Kang, M. J.; Song, W. J.; Han, A. R.; Choi, Y. S.; Jang, H. G.; Nam, W. W. *J. Org. Chem.* **2007**, *72*, 6301.

SCHEME 2. SDKIE for Rh(II)-Catalyzed C−C Bond Formation



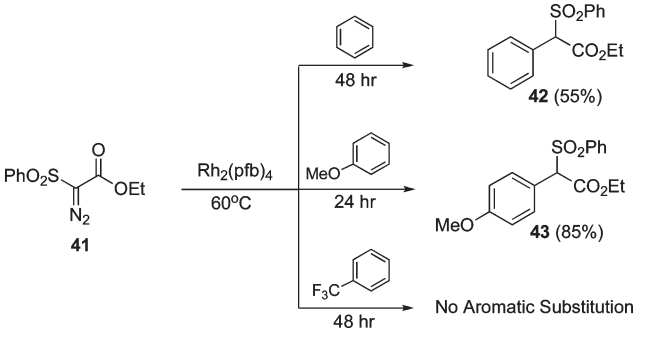
SCHEME 3. Plausible Mechanism for Rh(II)-Catalyzed Aromatic Reactions



generate the rhodium carbenoid **36** irreversibly.[20] We believe that the six-membered ring in the transition state would prefer adopting a boat-like configuration, unlike a chair-like configuration commonly observed with aliphatic substrates.[21] The amide functionality and aromatic region impose the restrictions of planarity on those regions of the molecule, allowing only the boat-like configuration (Figure 1) for attack by the aromatic π-electron to the rhodium carbenoid carbon. Aromaticity was restored via syn periplanar rhodium-facilitated hydrogen transfer from the aromatic carbon to the former carbenoid carbon. In the case of smaller α-substituents, cyclopropanation would be the favorable pathway because of the more reactive nature of carbenoids, as well as low steric effects. Intermediate **39** generated as a result of cyclopropanation would rearrange to generate cycloheptatriene products. The proposed mechanism was supported by kinetic isotope studies, as well as by the fact that no 7,5-bicyclic ring products were observed in the case of bulky and electron-rich carbenoids.

Intermolecular Formal Aromatic C−H Insertion of α-(Phenylsulfonyl)diazoacetester while Averting the Common Buchner Reaction. In the intermolecular reaction of rhodium carbenoids with aromatic substrates, only few examples were developed[22] or the Buchner reaction pathway with breaking

SCHEME 4. Intermolecular Aromatic Substitution of Rhodium-(II) Carbenoids



of aromatic resonance was reported. Encouraged by our results in the intramolecular system, we attempted intermolecular aromatic substitution using bulky electron-rich carbenoids, as shown in Scheme 4.

Reactions of benzene and α-(phenylsulfonyl)diazoacetester **41** took place smoothly to provide the desired compound **42** in 55% yield. Surprisingly, the reaction with anisole afforded an 85% yield of the para-substituted product **43**, because the methoxy group is the ortho-, para-directing group in electrophilic aromatic substitution. As anticipated, however, the reaction of trifluoromethylbenzene, substituted with an electron-deficient group, was not detected even at higher reaction temperature. These observations further validate our hypothesis that an electrophilic aromatic substitution is accelerated with the electron-rich aromatic system. The intermolecular reaction did not

(20) Wang, F. M.; Wang, J.; Hengge, A. C.; Wu, W. *Org. Lett.* **2007**, *9*, 1663 and references cited therein.

(21) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547.

(22) (a) Davies, H. M. L.; Smith, H. D.; Hu, B.; Klenzak, S. M.; Hegner, F. J. *J. Org. Chem.* **1992**, *57*, 6900. (b) Davies, H. M. L.; Jung, Q. *Org. Lett.* **2004**, *6*, 1769.

provide higher yield than the intramolecular reaction, since there was not an induced steric effect, such as *N*,*O*-acetal formation in the intramolecular reaction. However, based on our knowledge, this is the first example of rhodium-catalyzed intermolecular formal aromatic C−H insertion. Currently in progress are further studies focusing on intermolecular cross-coupling reactions with various diazocarbenoids, and their successful results will be reported in due course.

Conclusion

We have developed a protocol for the preparation of various isoquinolinones via a dirhodium(II)-catalyzed formal aromatic C−H insertion of six-membered systems that avoids the common Buchner reaction. The reactions occurred via an electrophilic aromatic substitution pathway rather than σ-bond metathesis, as indicated by an inverse secondary deuterium kinetic isotope effect. Six-membered-ring formations were successfully achieved by the use of sterically bulky and electron-rich carbenoids, including a phenylsulfonyl group or an ethoxyphosphoryl group. In addition, we have extended the scope of this methodology by including an intermolecular formal aromatic C−H insertion reaction, which has never been reported previously.

Experimental Section

General Procedure for the Intramolecular Electrophilic Aromatic Substitution of Diazoacetamides 1 and 3. A 50-mL two-necked flask equipped with a condenser was completely dried with a heat gun under flowing N_2. After the flask was cooled to room temperature, $Rh_2(pfb)_4$ (0.05 mmol) and diazoacetamide (1.0 mmol) were added under a gentle stream of nitrogen. Benzene (10 mL) was added, and the mixture was stirred at 60 °C under a N_2 atmosphere. After complete consumption of the diazoacetamide, benzene was evaporated. The insertion product was isolated by silica gel column chromatography.

2:. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.85−7.81 (m, 2H), 7.73−7.67 (m, 1H), 7.58−7.52 (m, 2H), 7.47−7.34 (m, 3H), 7.07 (d, J = 7.3 Hz, 1H), 5.06 (ABX, J = 6.3, 10.3 Hz, 1H), 4.92 (s, 1H), 4.60 (ABX, J = 6.3, 8.4 Hz, 1H), 3.80 (ABX, J = 8.5, 10.3 Hz, 1H), 1.69 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.66, 137.15, 134.98, 134.48, 130.92, 129.66, 129.20, 128.99, 128.28, 125.46, 123.94, 95.71, 74.51, 68.17, 58.14, 25.04, 23.22. MS (EI) m/z (%) 342 ([M − 15]$^+$, 4), 215 (100), 201 (33), 130 (71); HRMS-ESI (m/z) [M + H$^+$] calcd. for $C_{19}H_{20}NO_4S$ 358.1108, found 358.1115

10:. *Syn*: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.45−6.41 (m, 2H), 6.16−6.15 (m, 1H), 6.07 (d, J = 2.0 Hz, 1H), 5.32 (d, J = 9.6 Hz, 1H), 4.85 (ABX, J = 6.2, 9.6 Hz, 1H), 4.09 (ABX, J = 6.2, 7.8 Hz, 1H), 3.32 (s, 1H), 3.27 (ABX, J = 7.8, 9.2 Hz, 1H), 1.71 (s, 3H), 1.49 (s, 3H); 70%. *Anti*: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.47−6.45 (m, 2H), 6.14−6.12 (m, 1H), 6.05 (d, J = 2.0 Hz, 1H), 5.33 (d, J = 9.6 Hz, 1H), 4.77 (ABX, J = 6.2, 9.6 Hz, 1H), 4.15 (ABX, J = 6.2, 7.8 Hz, 1H), 3.52 (ABX, J = 7.8, 9.2 Hz, 1H), 3.20 (s, 1H), 1.73 (s, 3H), 1.48 (s, 3H); 30%

General Procedure for the Intermolecular Electrophilic Aromatic Substitution of Diazoacetamide 41. A 50-mL two-necked flask equipped with a condenser was completely dried with a heat gun under flowing N_2. After the flask was cooled to room temperature, $Rh_2(pfb)_4$ (0.10 mmol) and **41** (0.51 g, 2.00 mmol) were added under a gentle stream of nitrogen. Anisole (20 mL) was added, and the mixture was stirred at 60 °C under a N_2 atmosphere. After complete consumption of the diazoacetamide **41**, solvent was removed in vacuo. The insertion product **43** (85%) was isolated by silica gel column chromatography. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.65−7.57 (m, 3H), 7.47−7.40 (m, 2H), 7.30−7.24 (m, 2H), 6.84−6.79 (m, 2H), 5.04 (s, 1H), 4.26−4.12 (m, 2H), 3.79 (s, 3H), 1.21 (t, J = 7.3 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 164.95, 160.61, 136.46, 133.98, 131.50, 129.85, 128.47, 119.57, 113.92, 74.60, 62.35, 55.26, 13.82. MS (EI) m/z(%) 344 ([M]$^+$, 12), 193 (100), 165 (53), 109 (42); HRMS-ESI (m/z) [M + H$^+$] calcd for $C_{17}H_{19}O_5S$ 335.0948, found 335.0952

Acknowledgment. We acknowledge generous financial support from the National Institute of General Medical Sciences of the National Institute of Health (RO1 GM 62767 and GM 71495).

Supporting Information Available: Experimental details for the preparation of compounds and NMR spectra of these compounds, and crystallographic information for compounds **10**. This material is available free of charge via the Internet at http://pubs.acs.org.